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Status report covers progress made through the period

February 1, 1991 through May 31, 1991

on N00014-89-J-3124

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Metabolic Changes and Hemodynamic Dysfunction Following

Hypothermic Shock

Grant Number: N00014-89-J-3124

Harvey I Miller, Ph.D. - Principal Investigator

STATUS REPORT

From February 1, 1990 To May 31, 1991

Acute, severe, accidental hypothermia can produce a shock-like state which can subtly injure several organs. The manifestations of these injuries are difficult to observe because they may be masked by compensatory mechanisms. The resulting organ dysfunction can persist many hours past the return to normal body temperature. The severity of individual organ dysfunction is not always lethal, but coupled with the other organ changes, can jeopardize the survival of the victim. The purpose of these investigations is to uncover the mechanisms that produce the dysfunctions and determine appropriate therapeutic procedures to reverse this pathological process. We have shown that following immersion hypothermia and rewarm a cardiac dysfunction persists for at least 48 hours (see past status report). This dysfunction is not apparent in the whole intact animal because of cardiovascular compensatory mechanisms. However, if hearts from hypothermic animals are isolated and perfused, they exhibit depressed Starling curves. In other words, hearts from these hypothermically shocked animals have a decreased physiologic reserve. Catecholamines released in response to the stress of hypothermia contribute to this reserve when the contractility of the heart is decreased. They help maintain a sufficiently high blood pressure to perfuse the critical organs when the heart fails. However, even with catecholamine support, the heart fails when its temperature falls below some critical point and its own chemical production of energy is too low. This may result from a Q_{10} effect. It appears that after the body temperature has returned to normal, the catecholamines remain elevated for 4 to 24 hours without the usual adrenergic manifestations of: (1) elevated heart rate, (2) peripheral vasoconstriction and (3) elevated blood FFA and glucose levels. It would appear that the catecholamine sensitive organs have decreased sensitivity. This could be, in part, one mechanism of this cardiovascular failure. The question addressed in the studies done during the period described by this progress report was therefore "Is cardiovascular function compromised by the tissue being less sensitive to catecholamines?"

Progress was made in showing the myocardium was less sensitive to catecholamines following severe hypothermia and rewarm.

Guinea pigs, with indwelling catheters and thermistors, were temporarily anesthetized with a short acting barbiturate, Brevital®, and immersed neck-deep in ice-water until their core temperature fell to 25.5°C. The animal was then wrapped in a heating pad and warmed until the core temperature returned to 38.5°C. Observations were recorded and blood samples taken at various time intervals. In these experiments, some of the guinea pigs were anesthetized at 4 hours following return to normal core temperature. The hearts of these animals were excised and placed on a perfused working heart apparatus. We then tested the function of these hearts with a variety of preloads. After all measurements were made, isoproterenol was infused into the left atrium and dose response curves were constructed.

Rapid increases in blood pressure and heart rate are observed 10-20 seconds after exposure to cold. As the body temperature falls (Figure 1), so does blood pressure (Figure 2) and heart rate (Figure 3). The opposite is seen on rewarm, with normal values recorded after normal body temperature is attained. However, catecholamine levels remained elevated (Figure 4) for more than 4 hours after rewarm. Catecholamines levels elevated to this range would be expected to elevate the HR and blood pressure above normal, but did not.

In order to test the sensitivity of the adrenergic receptors of the myocardium, hearts of control (not cold immersed or rewarmed) and hypothermic-rewarmed guinea pigs were isolated and were infused at different dosages of isoproterenol. Control hearts showed no response at dosages up to 10^{-8} M. At 10^{-7} M, max dp/dt rose 10% and at 10^{-6} M it increased 40%. At 10^{-5} M, it had similar response as the concentration 10^{-6} M, with an increase in isolated spontaneous arrhythmias. Dosages higher than 10^{-5} M produced ventricular fibrillation (Figure 5). The max dp/dt of hearts from the hypothermic and rewarmed animals fell with doses from 10^{-11} to 10^{-8} when compared to the unstimulated state. When 10^{-7} M was applied, the hearts fibrillated. The same pattern was seen for cardiac output (Figure 6) and left ventricular peak systolic pressure [LVPSP] (Figure 7).

It appears that hearts of chilled and rewarmed guinea pigs are less sensitive to β-adrenergic stimulation; instead of stimulating increases in heart rate, blood pressure and contractility, it decreased it. The mechanism of this phenomenon is uncertain at this time. Also, a much smaller dose (10^{-7} M) produced fibrillation. It is interesting that this dose was the lowest effective dose in the controls. It would appear that the β-adrenergic receptors have down regulated due to saturation of the most sensitive ones. Also, synthesis of receptors may have been slowed because of the very low temperature . Some of the β-adrenergic effects of catecholamines have been muted by the combination of both these events. Thus, other adrenergic effects, usually obscured by β effectors may surface. However some of the less apparent effects, for example vasoconstriction of the coronary circulation, can surface and, in part, be responsible for the fibrillation seen in the hearts of the cooled animals. Since these are very preliminary results, many additional experiments with a variety of protocols will have to be done. In this way we will uncover the mechanisms of the cardiac dysfunction of severe accidental hypothermia.

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FIGURE 1

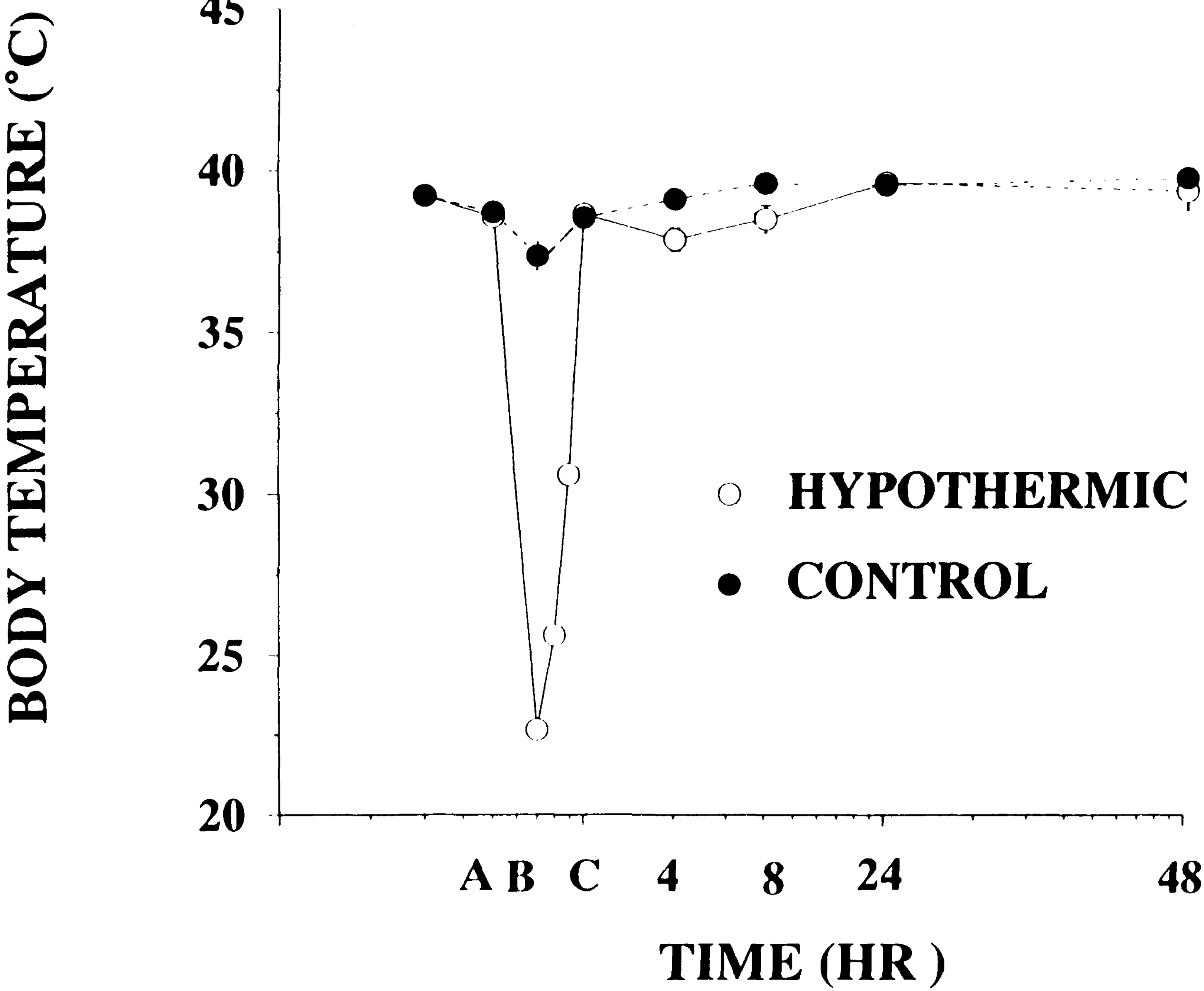
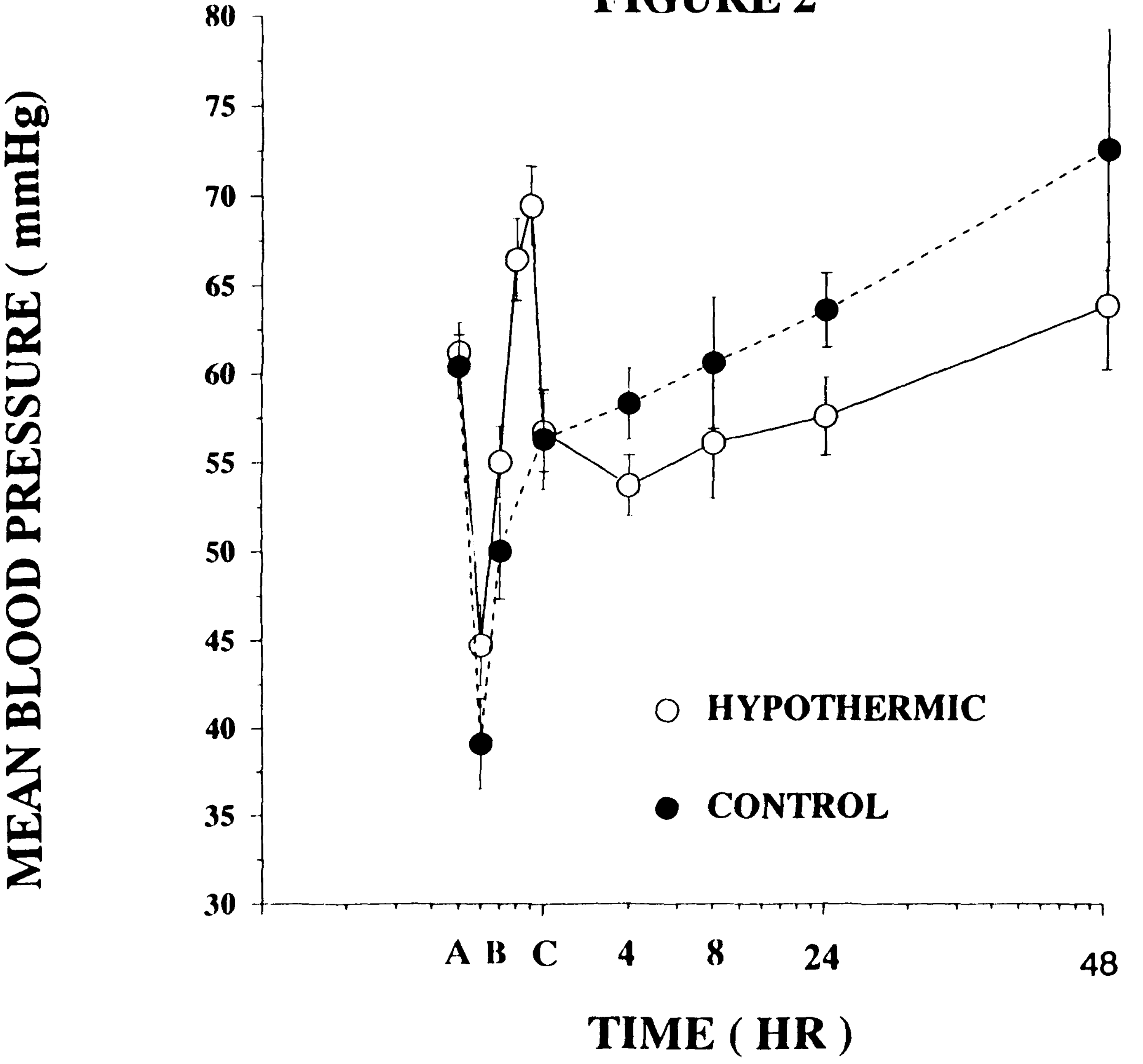
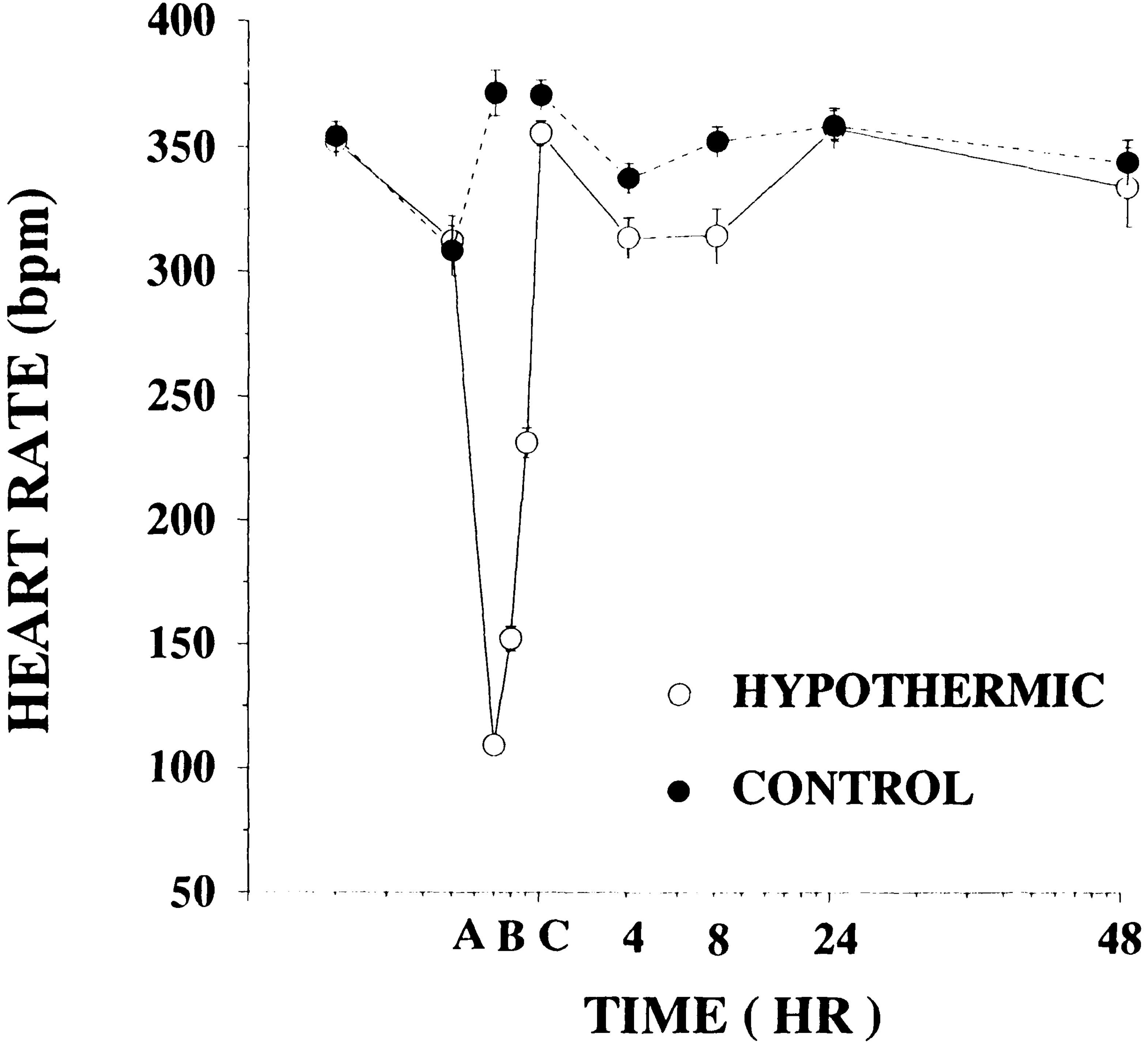

BODY TEMPERATURE (°C)
45
40
35
30
25
20
HYPOTHERMIC
CONTROL
A B C 4 8 24 48
TIME (HR)

FIGURE 2



MEAN BLOOD PRESSURE (mmHg)
80
75
70
65
60
55
50
45
40
35
30
HYPOTHERMIC
CONTROL
A B C 4 8 24 48
TIME (HR)

FIGURE 3



HEART RATE (bpm)
400
350
300
250
200
150
100
50
A B C
4
8
24
48
TIME (HR)
HYPOTHERMIC
CONTROL

FIGURE 4

CATECHOLAMINE

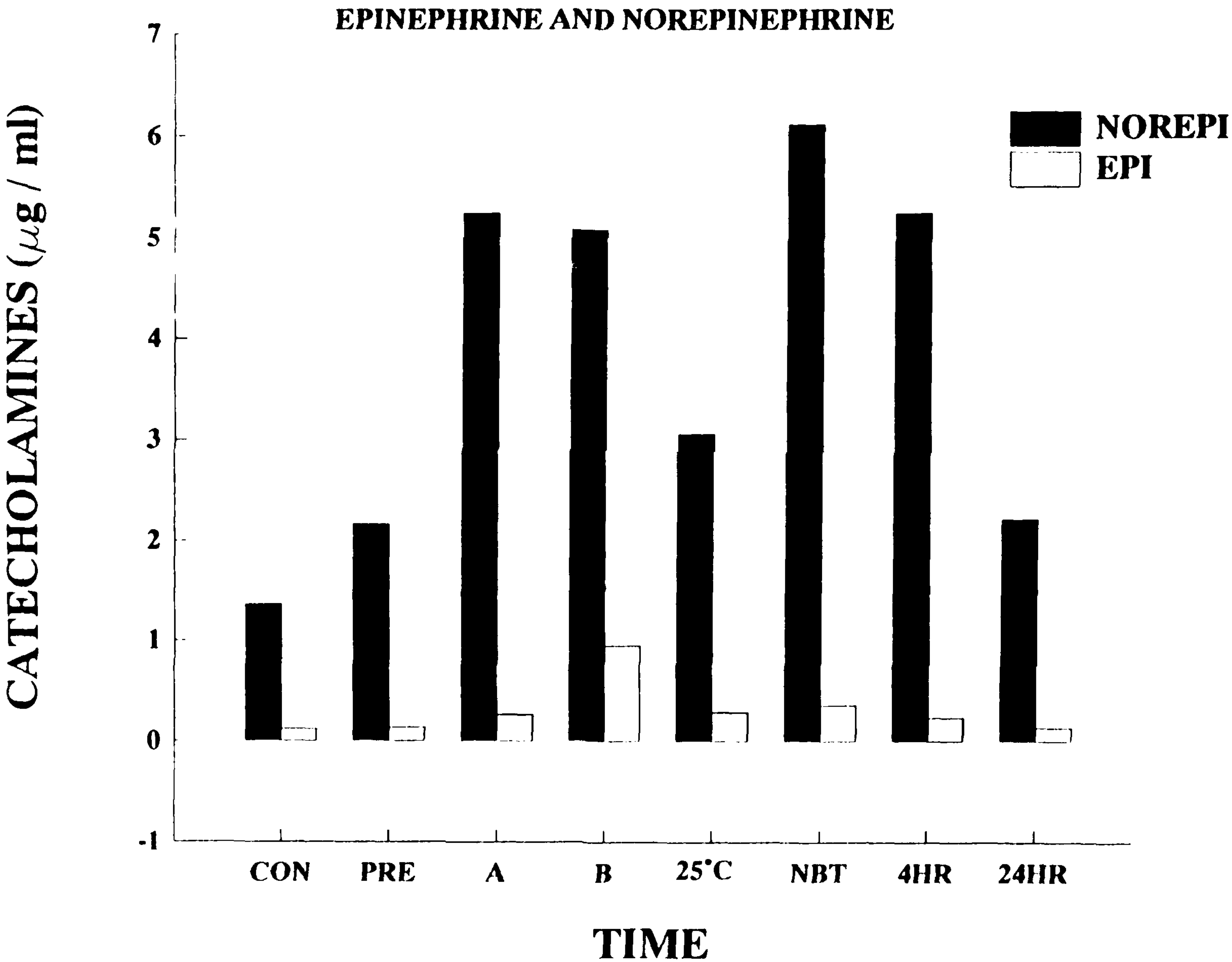


FIGURE 5

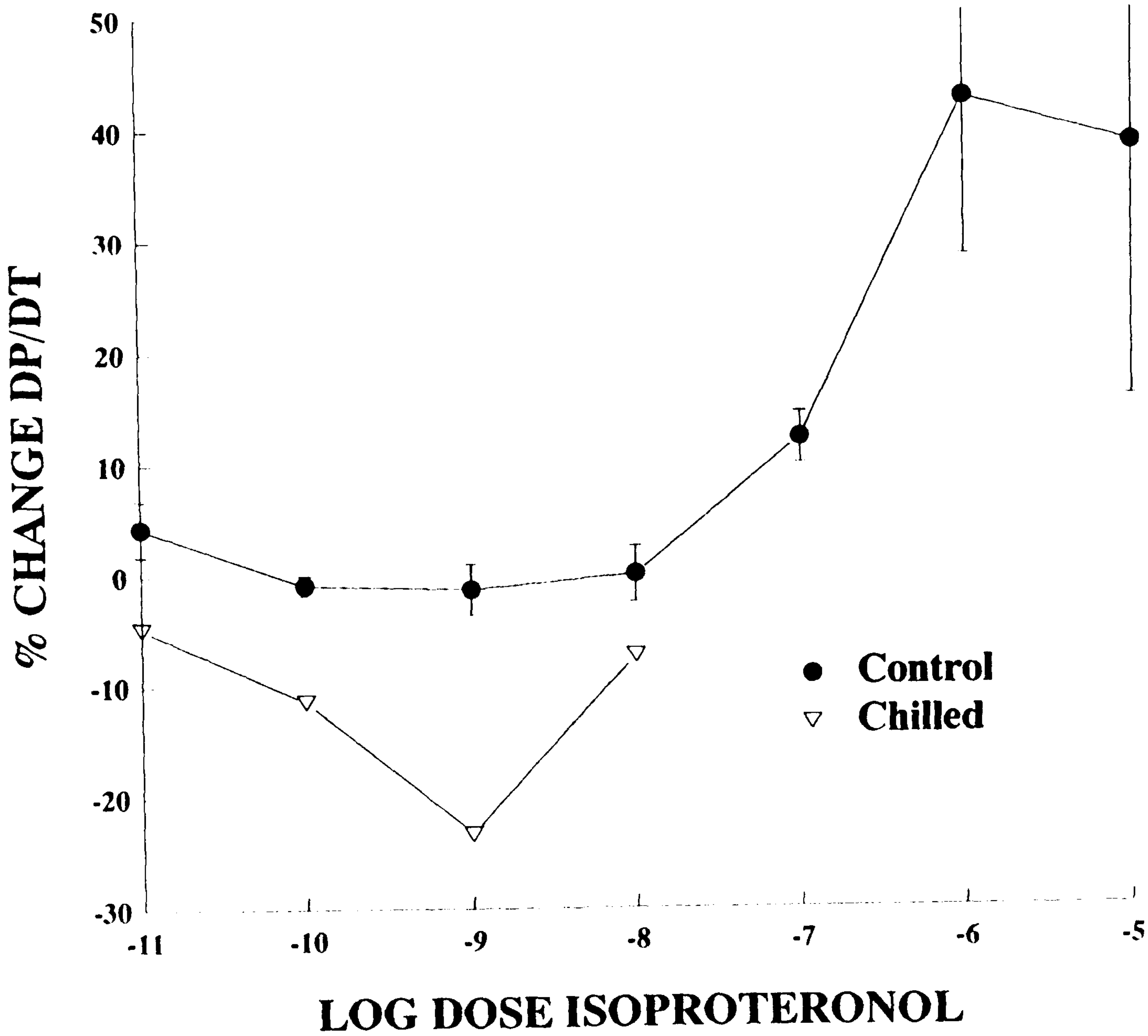
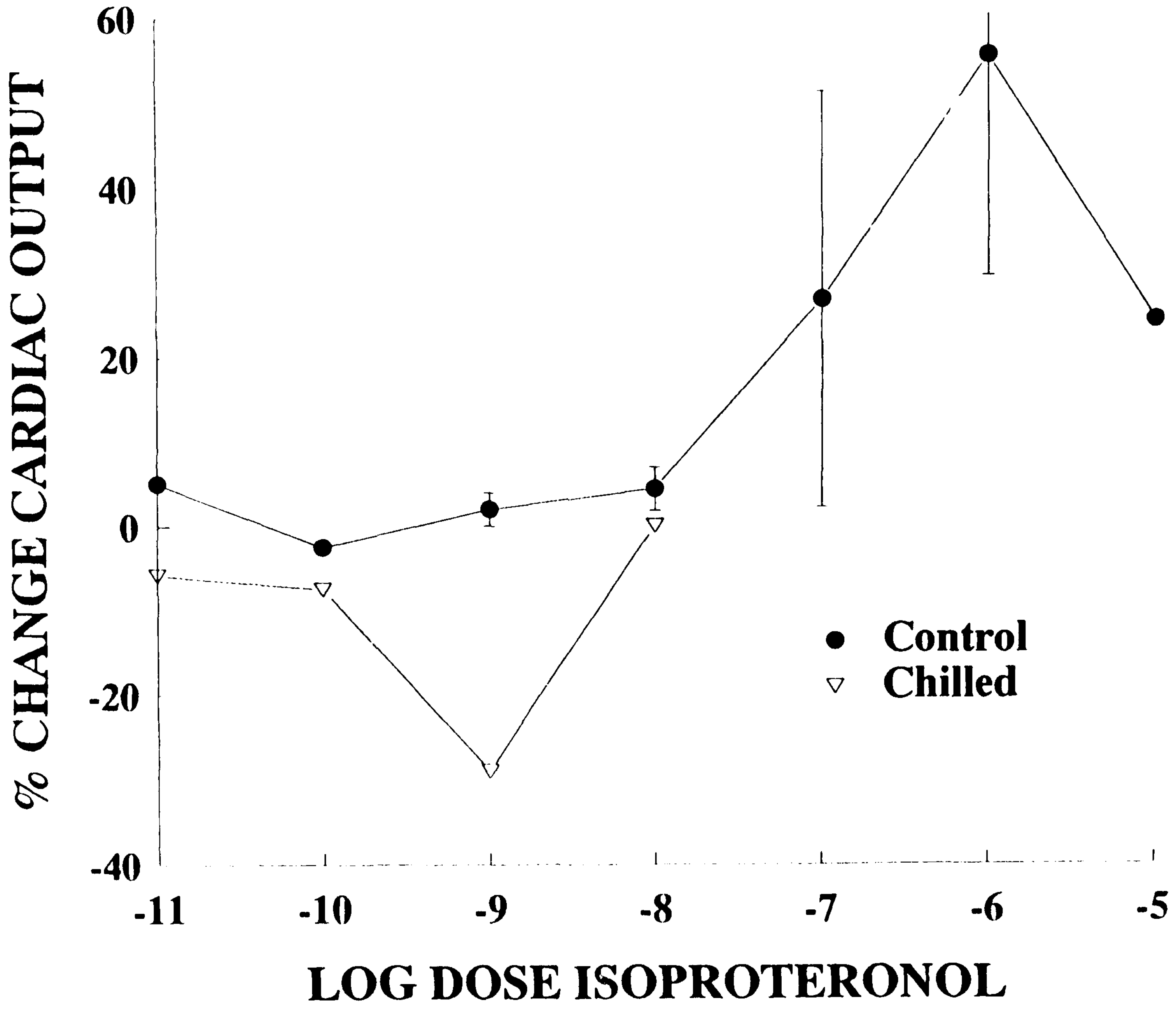
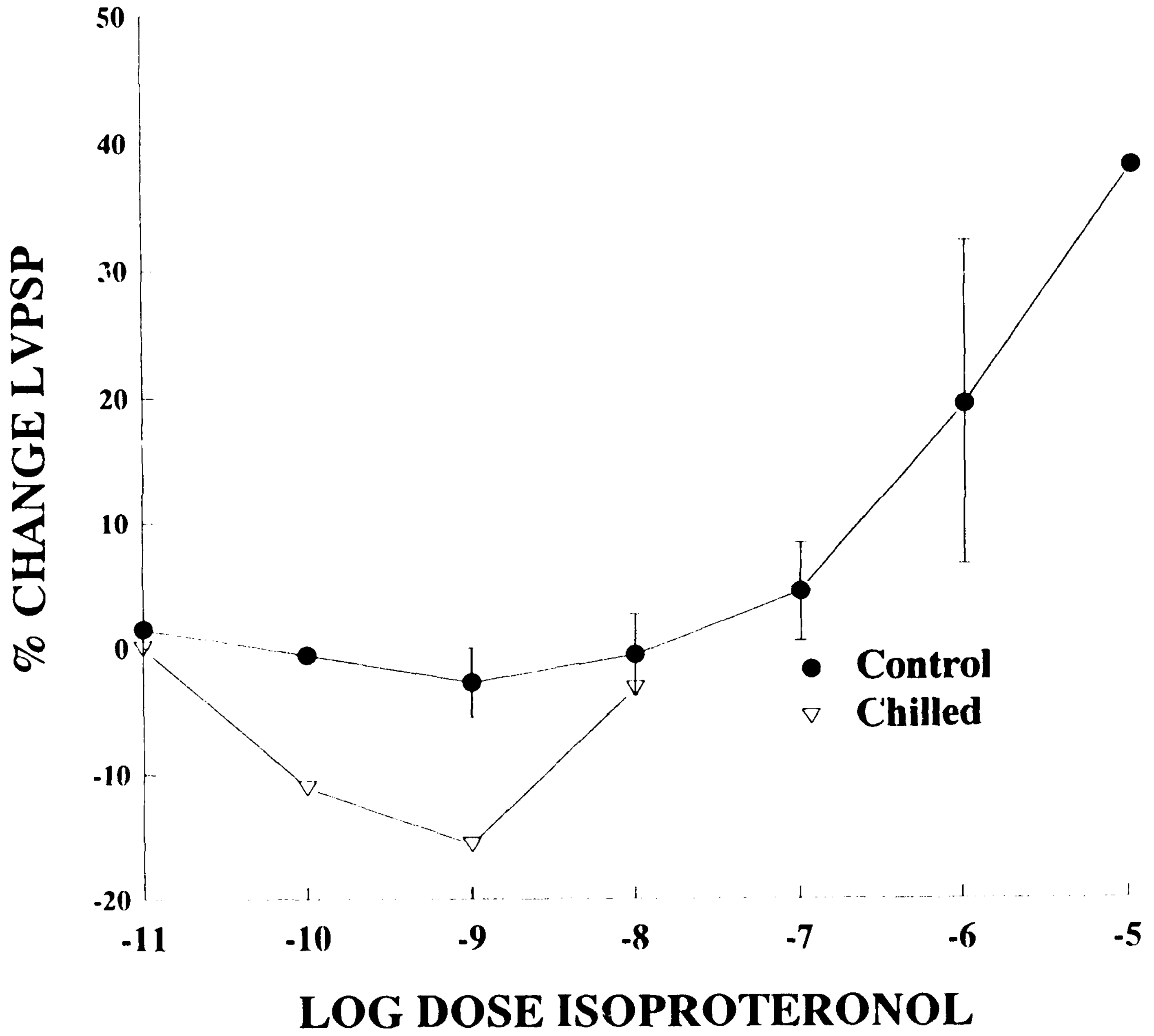

% CHANGE DP/DT
50
40
30
20
10
0
-10
-20
-30
-11
-10
-9
-8
-7
-6
-5
LOG DOSE ISOPROTERONOL
Control
Chilled

FIGURE 6



% CHANGE CARDIAC OUTPUT
60
40
20
0
-20
-40
-11
-10
-9
-8
-7
-6
-5
LOG DOSE ISOPROTERONOL
Control
Chilled

FIGURE 7



% CHANGE LVPSP
50
40
30
20
10
0
-10
-20
-11
-10
-9
-8
-7
-6
-5
LOG DOSE ISOPROTERONOL
Control
Chilled